

Iodine-containing radioactive sources

5 This invention relates to radiotherapy. More particularly it relates to radioactive sources for use in brachytherapy and to methods for the manufacture of such sources.

10 Brachytherapy is a general term covering medical treatment which involves placement of a radioactive source near a diseased tissue and may involve the temporary or permanent implantation or insertion of a radioactive source into the body of a patient. The radioactive source 15 is thereby located in proximity to the area of the body which is being treated. This has the advantage that the required dose of radiation may be delivered to the treatment site with relatively low dosages of radiation to surrounding or intervening healthy tissue.

20 Brachytherapy has been proposed for use in the treatment of a variety of conditions, including arthritis and cancer, for example breast, brain, liver and ovarian cancer and especially prostate cancer in men (see for 25 example J.C. Blasko et al., *The Urological Clinics of North America*, **23**, 633-650 (1996), and H. Ragde et al., *Cancer*, **80**, 442-453 (1997)). Prostate cancer is the most common form of malignancy in men in the USA, with more than 44,000 deaths in 1995 alone. Treatment may involve 30 the temporary implantation of a radioactive source for a calculated period, followed by its removal.

Alternatively, the radioactive source may be permanently implanted in the patient and left to decay to an inert state over a predictable time. The use of temporary or 35 permanent implantation depends on the isotope selected and the duration and intensity of treatment required.

Permanent implants for prostate treatment comprise radioisotopes with relatively short half lives and lower energies relative to temporary sources. Examples of permanently implantable sources include iodine-125 or 5 palladium-103 as the radioisotope. The radioisotope is generally encapsulated in a titanium casing to form a "seed" which is then implanted. Temporary implants for the treatment of prostate cancer may involve iridium-192 as the radioisotope.

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Recently, brachytherapy has also been proposed for the treatment of restenosis (for reviews see R. Waksman, *Vascular Radiotherapy Monitor*, 1998, 1, 10-18, and *MedPro Month*, January 1998, pages 26-32). Restenosis is a 15 renarrowing of the blood vessels after initial treatment of coronary artery disease.

Coronary artery disease is a condition resulting from the narrowing or blockage of the coronary arteries, known 20 as stenosis, which can be due to many factors including the formation of atherosclerotic plaques within the arteries. Such blockages or narrowing may be treated by mechanical removal of the plaque or by insertion of stents to hold the artery open. One of the most common forms of 25 treatment is percutaneous transluminal coronary angioplasty (PTCA) - also known as balloon angioplasty. At present, over half a million PTCA procedures are performed annually in the USA alone. In PTCA, a catheter having an inflatable balloon at its distal end is inserted 30 into the coronary artery and positioned at the site of the blockage or narrowing. The balloon is then inflated which leads to flattening of the plaque against the artery wall and stretching of the artery wall, resulting in 35 enlargement of the intraluminal passage way and hence increased blood flow.

PTCA has a high initial success rate but 30-50% of patients present themselves with stenotic recurrence of the disease, i.e. restenosis, within 6 months. One treatment for restenosis which has been proposed is the 5 use of intraluminal radiation therapy. Various isotopes including iridium-192, strontium-90, yttrium-90, phosphorus-32, rhenium-186 and rhenium-188 have been proposed for use in treating restenosis.

10 Conventional radioactive sources for use in brachytherapy include so-called seeds, which are sealed containers, for example of titanium or stainless steel, containing a radioisotope within a sealed chamber but permitting radiation to exit through the container/chamber 15 walls (US-A-4323055 and US-A-3351049). Such seeds are only suitable for use with radioisotopes which emit radiation which can penetrate the chamber/container walls. Therefore, such seeds are generally used with radioisotopes which emit γ -radiation or low-energy X-rays, 20 rather than with β -emitting radioisotopes.

Brachytherapy seeds comprising a coating of radioactive silver iodide on a silver wire encapsulated inside a titanium container are known in the art (US-A-25 4323055). Such seeds provide radiation emission which is equivalent to between 0.1 and 100 millicuries of radioactivity. Such seeds are available commercially from Medi-Physics, Inc., under the Trade Name I-125 Seed® Model No. 6711.

30 Other conventional brachytherapy seeds comprise titanium containers encapsulating ion exchange resin beads onto which a radioactive ion, for example I-125, has been adsorbed (US-A-3351049). The immobilisation of a 35 radioactive powder within a polymeric matrix has also been proposed (WO97/19706).

GB-A 1187368, US-A 4729903, WO99/41755 and WO99/40970 disclose the adsorption of molecular iodine-125 onto various substrates including graphite and zeolites. However, there are safety implications with working with 5 iodine-125 in the form of molecular iodine due to its volatility. The use of volatile radioisotopes can give rise to radiation hazards during manufacture of radioactive sources or if a radioactive seed ruptures during handling.

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US-A-4323055 discloses activities for iodine-125 containing seeds of up to 100 mCi/seed, and iodine-125 containing seeds based on metal wires have not demonstrated the ability to carry very high levels of 15 radioactivity. With radioactive seeds based on metal wires there is also the disadvantage that some of the radioactivity is absorbed by the wire itself. The amount of radioactivity absorbed by the wire increases as the atomic number of the metal used to form the wire increases. 20 The precise amount of attenuation will be a function of the dimensions of the wire. For example, with a silver iodide-125 coated 0.5 mm diameter silver wire, up to about 20% of the radioactivity is absorbed by the wire itself. To manufacture a radioactive seed of a given 25 external radiation dose, extra radioactivity must be loaded onto the wire to take into account the absorption of some of the activity by the wire and also by the seed container. As the desired activity of the seed increases, so does the cost of the extra percentage amount of 30 radioactivity which must be loaded onto the wire.

Attempts to manufacture high activity radioactive seeds comprising radioactive anions adsorbed onto ion exchange resin beads as in US-A-3351049 have not been 35 completely successful, due we believe to the adverse effect of the radiation on the polymer bonds of the beads

themselves. We have found there to be a tendency for the beads to degrade under the influence of high levels of radioactivity, leading to unreliable results.

5 There is still a need for a high activity radioactive source which is suitable for use in brachytherapy and which does not give rise to safety problems inherent in the use of radioactive molecular iodine, and for methods to manufacture such sources. Such sources may be useful
10 for the temporary brachytherapy of cancers and proliferative diseases, and especially for the prevention of restenosis following PTCA.

As one aspect of the invention there is therefore
15 provided a radioactive source suitable for use in brachytherapy, preferably a sealed source, comprising a radioactive isotope of iodine in the form of iodide ions or an iodine-containing compound adsorbed on the surface of a substantially non-radiation attenuating substrate,
20 with the proviso that when the iodine is in the form of iodide ions, then the substrate is not an ion exchange resin. Preferably, the source has an activity in the range of about 0.1 mCi to about 1200 mCi. Preferably for use in the treatment of restenosis, the source has an
25 activity in the range of about 200 mCi to about 1200 mCi, preferably 300 mCi to 1000 mCi, and more preferably 400 mCi to 600 mCi. Preferred sources for use in prostate brachytherapy have an activity in the range of about 0.1 mCi to about 5 mCi, more preferably about 0.2 to about
30 2 mCi.

Suitable radioisotopes of iodine are iodine-125, iodine-131 and iodine-123. Preferred due to its longer half life is iodine-125. As used herein, wherever the
35 term iodine-125 is used, this should be interpreted as being also applicable to iodine-131 or iodine-123.

The radioisotope of iodine may be present in the form of iodide ions or in the form of an iodine-containing compound. As used herein, the term "iodine-containing compound" includes any compound containing covalently bonded iodine where the iodine is bonded to at least one other atom which is not a halogen. It does not therefore include molecular iodine (I_2) or iodohalogens such as ICl . Examples of suitable compounds include an organic compound containing a carbon-iodine bond, an iodoso-compound such as iodosobenzene, phenyliodoso diacetate, and o-iodosobenzoic acid, a diaryliodinium salt such as diphenyliodinium bromide and diphenyliodinium iodide wherein either or both of the iodine atoms may be a radioisotope of iodine, an N-iodoamide such as N-iodosuccinimide, an iodoxyaryl compound such as iodoxybenzene, or a covalently bound inorganic iodine compound such as tributyltin iodide. Preferred iodine-containing compounds are non-volatile.

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Preferably, the sources of the invention comprise a sealed container, for example a substantially cylindrical tubular container made of metal or some other suitable material, having a cavity in which a suitable amount of iodine-125 is present.

The container material should be corrosion resistant, compatible with body fluids and non-toxic and should not unduly absorb the X-ray radiation emitted from the radioisotope. Suitable containers include those made of low atomic numbered metals such as titanium or stainless steel. Higher atomic number metals such as gold, copper or platinum result in too much radiation attenuation to be useful *per se*. However, they may be useful for plating over certain low atomic number metals such as beryllium which would otherwise be too toxic if used without an

outer coating. Titanium, titanium alloys or stainless steel are preferred metals for the container. Other suitable container materials include inert synthetic materials, for example Teflon™. The container is 5 preferably completely sealed inside so there is no danger of leakage.

The source should be of an overall size and dimensions suitable for its intended use. For example, 10 the overall dimensions of each radioactive source should preferably be such that it can be delivered to the treatment site using conventional techniques, for example it can be loaded inside a conventional catheter for delivery to the site of restenosis. Seeds for use in the 15 treatment of prostate cancer, for example, are typically substantially cylindrical in shape and approximately 4.5 mm long with a diameter of approximately 0.8 mm, such that they may be delivered to the treatment site using a hypodermic needle. For use in the treatment of 20 restenosis, a source should be of suitable dimensions to be inserted inside a coronary artery, for example with a length of about 10 mm and a diameter of about 1 mm, preferably a length of about 5 mm and a diameter of about 0.8 mm, and most preferably with a length of about 3 mm 25 and a diameter of about 0.6 mm. Sources for use in the treatment of restenosis are typically delivered to the treatment site using conventional catheter methodology.

The substrate may be any material which is able to 30 adsorb iodide ions or an iodine-containing compound (either by physisorption or by chemisorption) and which is sufficiently stable to radiation to allow processing of the substrate into a brachytherapy source once the iodine radioisotope has been adsorbed. Preferably, the substrate 35 is in the form of a substantially rigid body, for example a rod, filament or sphere. Preferably, the substrate has

a large surface area available for adsorption. The substrate may also be in powdered form.

The substrate should be substantially non-radiation attenuating. Preferably, the substrate comprises at least 5 60% by volume, more preferably at least 80% by volume and most preferably at least 90% by volume of atoms of elements of low atomic number. The atoms may be present in elemental form, or in mixtures or compounds. As used 10 herein, a low atomic number is preferably an atomic number ≤ 30 , and more preferably ≤ 25 . Preferred substrates contain a minimal amount (e.g. as a coating only) of high atomic number, radiation-attenuating materials such as the metals silver, gold or palladium. In such substrates, the 15 minimal amount is that sufficient to permit production of the radioiodine coating. For example, the substrate may comprise a substantially non-radiation attenuating material coated with a thin layer of a metal such as silver.

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The iodide ions or iodine-containing compound should be coated on the surface of the substrate only, rather than being uniformly distributed throughout the body of the substrate. The radioiodine being present as a coating 25 on the surface of the substrate also helps to minimise attenuation of the radiation.

One of the main purposes of using substrates comprising materials of high atomic number in 30 brachytherapy sources such as seeds has traditionally been to permit visualisation of the location of the seed *in vivo* post-implantation by X-ray. Preferably, the sources of the invention comprise a biocompatible container which is sufficiently echogenic such that the source may be 35 visualised *in vivo* by ultrasound rather than by X-ray. The use of substrates comprising materials of high atomic

number is then no longer necessary in order to permit visualisation of the seed.

As a further aspect of the invention there is
5 therefore provided a radioactive source suitable for use
in brachytherapy comprising a radioactive isotope of
iodine in the form of iodide ions or an iodine-containing
compound adsorbed on the surface of a substantially non-
radiation attenuating substrate, the radioisotope and the
10 substrate being sealed inside a biocompatible echogenic
container.

The iodide ions or the iodine-containing compounds
may be physically adsorbed on the surface of the substrate
15 (physisorption) or there may be some degree of chemical
bonding between the substrate and the iodide ions or
iodine-containing compound (chemisorption): chemisorption
is preferred rather than physisorption.

20 Suitable substrates include carbon, alumina, titanium
oxides, silica and silicon oxides, zeolite-type trivalent
metal silicates, metal phosphates and hydroxyphosphates
including hydroxyapatite, calcium hydroxyapatite, glassy
materials, aluminium nitride, ceramics, radiation
25 resistant polymers and natural materials such as bone,
coral, coal, limestone, cellulose, starch, agar, gelatin,
chitin, and hair either alone or woven together to make
more substantial rods.

30 A preferred substrate is carbon, and in particular
activated carbon. Suitable activated carbon is available
in the form of activated charcoal from American Norit Co.,
Inc. under the trade names Darco® and Norit®. Preferably
the substrate comprises atoms of elements of low atomic
35 number such that the absorption of radioactivity by the
substrate is minimized. Preferably, the substrate is also

of low density to help minimize absorption of radiation. For these reasons, carbon is particularly preferred.

For the adsorption of iodide ions, positively charged substrates are preferred. For example, ceramics at a pH below their isoelectric point (i.e. their pI) will express a positive surface charge which will attract negatively charged iodide anions.

If the substrate is carbon, it may be in the form of a filament, rod, sphere, powder, particles, dust, compressed powder, carbonized polymers including starch, cellulose, chitin, agar or gelatin, carbon yarn available from Alpha Aesar, and carbonized polymers derived from acetylene, charcoal, soot or graphite including graphite fibres and rods, or a clathrate, fullerene or other carbon cage.

An organic compound which adsorbs onto the chosen substrate may be iodinated with ^{125}I and the radioiodinated compound then adsorbed onto the substrate. Organic compounds which adsorb onto a desired substrate may be known in the art or may be identified using routine experimentation.

Any known method for the iodination of organic compounds may potentially be adapted to use a radioactive isotope of iodine in place of a "cold" isotope. For example, iodide can be reacted with an organic molecule to form a bond between the iodide atom and a carbon atom on that molecule. For example, radioactive sodium iodide can be reacted with tyrosine to afford radiolabelled tyrosine. In addition, methods for the covalent attachment of radioisotopes of iodine to organic molecules are known in the art, for example in Parker, C.W. "Radiolabelling of Proteins" in Methods in Enzymology, Vol. 182, 721 (1990);

Noel, J-P. "La synthese radioactive avec le carbone 14, le tritium, le soufre 35 et l'iode 125, L'Act. Chim. (R), 1997, 7, 5-13. (Radioactive synthesis with carbon 14, tritium, sulfur 35 and iodine 125. Actual. Chim (1997), 5 (7), 5-13); Scherberg N.H. and Refetoff S. "Radioiodine Labelling of Ribopolymers for Special Applications in Biology", Methods in Cell Biology (1975) 10, pages 343-359 (Chaptern 19); and Baldwin, R.M., "Chemistry of Radioiodine", Appl. Radiat. Isot. Vol. 37, No.8, pp 817-10 821, 1986, all of which are incorporated by reference. Reagents and methods useful for radioiodination of organic molecules can also be found in the Pierce Catalog and Handbook, e.g., 1994-1995 edition, page T-335, Technical Section, "Iodination" (incorporated by reference).

15 Preferred organic compounds for iodination include tyrosine phenylalanine either alone or as a dimer or polymer, tyrosine, phenylalanine containing peptides and proteins, phenols, and aromatic molecules with a reactive site for iodination; hydroxyaromatic compounds capable of 20 enol-keto type tautomerism such as a phenolic compound containing a hydrogen in the ortho- or para-position, for example catechol or poly(3,4-dihydroxystyrene) which can be prepared by latex polymerization or by limited coalescence free radical polymerization of 1-vinyl-3,4-25 methoxystyrene followed by treatment with boron tribromide at low temperatures in methylene chloride; and aryl diazonium compounds which are known to form aryl iodides in a Sandmeyer-type reaction in the presence of potassium iodide (see Lucas H.J. and Kennedy E.R., Org. 30 Syn., Coll. Vol. 2, 351, 1943 (incorporated by reference)), for example the diazonium salt of anthranilic acid can provide diiodobenzene according to the method of Friedman L. and Logullo F.M., Angew. Chem., 77, 217, 1965 (incorporated by reference).

The substrate is preferably of a suitable size and dimensions to fit inside a container to form a sealed source. For example, the substrate may be rod-like or substantially spherical. However, the substrate may be 5 any size or shape suitable for irradiating the lumen of occluded blood vessels for the prevention of restenosis, and the size and shape of the container may be chosen depending on the dimensions of the substrate. A source 10 may comprise one or more substrates, or a plurality of substrates combined together, for example by compression and/or use of a suitable binder.

A plurality of substrates may be combined, optionally with the use of a binder. A binder is a material that can 15 bind two or more activated substrates or a plurality of substrates together to form a larger composite.

A binder may be cohesive agent such as a glue, for example crazy glue and its approved medical grade 20 counterpart Dermabond™, available from Ethicon, and other polymerised cyanoacrylate esters, an adhesive such as a hot melt adhesive, or a polymer such as polyvinyl alcohol, polyvinyl acetate, poly(ethylene-co-vinyl acetate) and partially hydrolyzed poly(ethylene-co-vinyl acetate) 25 polymers, polyvinylpyrrolidone or polyvinyl chloride. Also useful as binders are carbohydrates such as sucrose, mannitol, lactose, and the like, dextran, and cyclodextran; amino acids and proteins such as albumin; and salts such as alkali metal and alkaline earth metal 30 salts of halides, sulfates, phosphates, and nitrates. Binders comprising lower atomic weight elements are preferred in order to minimize the attenuation of radioactivity by the binder.

35 Preferably, the substrate body is in the form of a rod. A single container may contain only one substrate

which occupies substantially all of the cavity inside the container. Alternatively, each container may contain two or more substrates, for example optionally separated by a suitable spacer. Preferably, the substrate arrangement 5 will be such that there is a uniform radiation field around the source.

The level of radioactivity of a substrate prepared using the method of the invention will depend in part on 10 the amount of radioactive iodine used in the method. The amount of iodine-125 required to provide a source of given activity will depend in part on the amount of radiation absorbed by the substrate and by the container. The amount of attenuation in any given case can be readily 15 determined by a skilled person, for example by trial and error experimentation or by calculation.

The sources of the invention may be prepared by exposing a suitable substrate to a source of iodide ions 20 or an iodine containing compound, for example an ^{125}I -containing organic compound. For reasons of safety, it is preferred not to use volatile radioiodine-containing compounds, or isotopic precursors therefor.

25 As a further feature of the invention there is therefore provided a method for preparing a substrate suitable for use in a brachytherapy source, the method comprising exposing a substantially non-radiation attenuating substrate to a source of iodide-125 ions or an 30 iodine-125 containing compound such that the iodide ions or the iodine-125 containing compound is adsorbed onto the surface of the substrate, with the proviso that when the iodine is in the form of iodide ions, then the substrate is not an ion exchange resin. Preferably, the iodine-125 35 containing compound is an ^{125}I -containing organic compound.

The iodide ions may be present as a solution of a soluble iodide salt in a suitable solvent, for example a solution of potassium or sodium iodide-125 in water. Preferably, an aqueous solution of iodide-125 ions is 5 used.

Pegylated substrates, such as Eichrom's ABEC® (Aqueous Biphasic Extraction Chromatography) resins, may be used to selectively adsorb iodine (in the form of 10 iodide) from concentrated solutions of certain salts. Once loaded with iodine and dried, the substrates may be encapsulated in a container to form a brachytherapy source.

15 The iodine-125 containing compound may be present in solution in a suitable solvent. Alternatively, if the compound is a liquid it may be used neat. The substrate may alternatively be exposed to a vapour of an ¹²⁵I-containing organic compound, but this method is not 20 preferred for reasons of safety when working with radioactive compounds.

25 The substrate should be exposed to the iodide ions or to the iodine-containing compound for a sufficient period of time for the desired level of radioactivity to adsorb onto each substrate. Suitable exposure times may be determined by routine experimentation, for example by monitoring the level of non-adsorbed radioactive iodine remaining in the reaction medium.

30 If the iodine is in the form of an iodine-containing organic compound, the adsorption may take place in the same reaction vessel as the iodination reaction. For example, the substrate may be added to the reaction 35 mixture after the iodination reaction has occurred such that the iodinated product is adsorbed onto the substrate

without the need for any isolation of the iodinated product. The substrates onto which the iodine-125 has been adsorbed may then be isolated from the reaction mixture, for example by filtration, dried if necessary and 5 loaded into suitable containers to form radioactive sources for use in brachytherapy.

After the adsorption, the substrate may be further processed if required. For example, a plurality of 10 substrates may be formed into a composite by the application of pressure and/or by the use of a binder. In one aspect of the invention, low melting binders may be melted and mixed with an activated carbon substrate containing adsorbed iodine-containing molecules, and then 15 molded, cast or formed into a desired shape such as a thin rod, pellet, strip, wire, annulus or tube, and then cooled. The temperature should be below any temperature at which any substantial amount of iodine-125 containing compound might de-adsorb from the activated carbon. In 20 another aspect of the invention, the binder may be mixed with an activated carbon substrate containing adsorbed iodine-containing molecules, and then moulded, cast or formed into a desired shape under pressure.

25 If the substrate comprises a coating of silver ions or ions of some other metal which forms an insoluble iodide salt, the substrate may be exposed to a solution of iodide-125, for example a solution of Na^{125}I , such that an insoluble iodide salt coating will form on the surface of 30 the substantially non-radiation attenuating substrate. Such a method comprises a further feature of the invention. Substrates comprising a coating of silver ions include substrates such as polyvinyl alcohol, agar, gelatin, silica, carbonaceous materials or carbon yarn 35 which have been previously exposed to a source of silver ions, for example to a solution of a silver salt.

Preferably, a sufficient amount of radioactive iodine is used in the method of the invention to produce substrates with activity levels in the range of about 0.1 5 mCi to about 1 Curie. Such substrates may, for example, be incorporated into radioactive sources for use in brachytherapy which have an activity of about 0.1 mCi to about 900 mCi.

10 In order for substantially all of the radioactive iodine to adsorb onto the surface of the substrate, the substrate and the reaction medium are preferably agitated. Preferably, the agitation takes the form of rotation of the reaction vessel such that the substrates "tumble" or 15 roll in the reaction medium with each rotation.

For example, if the reaction vessel comprises a sealed individual vial, the vial may be rotated vertically end over end such that the contents tumble from end to end 20 of the vial with each rotation. Rotation at a speed of 20 to 60 rpm is suitable.

Alternatively, the reaction vessel may be rotated at an angle to the horizontal such that the substrate rolls 25 over in the reaction medium on each rotation. An angle of approximately 30° is suitable.

Suitable agitation of the reaction mixture also helps to ensure that maximum iodine uptake occurs, and that the 30 uptake is uniform over the entire surface of the substrate.

The radioactive sources of the invention may be used as temporary implants for the treatment of cancers, for 35 example head and neck cancers, melanoma, brain cancers, non-small cell lung cancer, breast cancer and ovarian,

uterine and cervical cancer and other diseases including proliferative diseases, arthritis, urethral stricture and fibroid uterine tumours. Due to their high levels of radioactivity, it is unlikely that the sources will be 5 useful for permanent implantation brachytherapy. The sources may also be useful in the prevention of restenosis following PTCA.

As a further aspect of the invention there is 10 provided a method of treatment of a condition which is responsive to radiation therapy, for example cancer and especially restenosis, which comprises the temporary placement of a radioactive source comprising an amount of iodine-125 adsorbed in the form of iodide ions or an 15 iodine-containing compound on the surface of a substantially non-radiation attenuating substrate, with the proviso that the substrate is not an ion exchange resin, at the site to be treated within a patient for a sufficient period of time to deliver a therapeutically 20 effective dose.

Preferably, the method of treatment of the invention is employed to inhibit restenosis at a site within the 25 vascular system of a patient which has previously been subjected to PTCA.

The invention will be further illustrated by the following non-limiting Examples.

Example 1Precipitation of Silver Iodide onto polyvinyl alcohol
(Ivalon) Particles

5 In a small beaker, 1 g of PVA particles (150-250 microns) was equilibrated with a 0.5 molar solution of silver nitrate for 1 hour. At the end of the hour, the particles were allowed to settle to the bottom of the beaker and the 10 supernatant was decanted to be replaced with 50 ml of distilled water. The particles were rinsed 3 times this way to prepare them for the final step. After decanting as much water as possible after the 3rd rinse, the particles were equilibrated with a solution of potassium 15 iodide for 1 hour. Afterwards, the particles were again rinsed with water and then suspended in a small volume of saline for further testing.

20 A 1 ml HPLC sample tube was used to transport the sample to the Center for Imaging and Pharmaceutical Research (CIPR) at the Massachusetts General Hospital for imaging in a Toshiba CT scanner at 80 kV. This initial sample of PVA with AgI precipitated onto it was measured as 441 Hounsfield Units (HU) in saline. The conventional wisdom 25 is that every 35 HU = 1 mg silver iodide or approximately 0.5 mg of iodide, and thus it can be estimated that 6.6 mg of iodide/ml of close packed particles is present in this sample or approximately 50 µg of iodide per particle. At a specific activity of 12 Curies/mg, each particle would 30 have approximately 600 mCurie of radiation on board.

Example 2Multiple Precipitations onto Polyvinyl alcohol (Ivalon) Particles

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A suspension of polyvinyl alcohol (PVA) particles was prepared as in Example 1 above. At the end of the water rinse after the addition of potassium iodide, the particles were again exposed to a solution of silver nitrate for another hour. The suspension was then rinsed with water before a second aliquot of potassium iodide was added to precipitate a second layer of silver iodide. This was then repeated for a portion of the sample for a third precipitation of silver iodide onto the PVA particles. The particles were imaged at Massachusetts General Hospital with the following results:

Preparation	Contrast of Saline (Hounsfield Units)	Estimated μg I/particle	Activity * mCi/part
AgI (1)	441	50	600
AgI (2)	1758	200	2400
AgI (3)	2434	275	3300

* assuming 12 Curies/mg specific activity of ^{125}I .

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Thus, it is clear that multiple layers of silver iodide can be deposited onto the PVA particles to obtain a wide range of iodide loadings and activities.

25

Example 3Precipitation of AgI onto a zeolite

Zeolites containing silver ions were purchased from Aldrich as 1.6 mm pellets and 20 mesh spheres with a

composition of $\text{Ag}_{7.6}\text{Na}_{0.4}[(\text{AlO}_2)_8(\text{SiO}_2)_{40}]$ and $\text{Ag}_{84}\text{Na}_2[(\text{AlO}_2)_{86}(\text{SiO}_2)_{106}]$, respectively. Upon exposure of these ceramic materials to a solution of sodium iodide, they changed in appearance from a silver colour to a 5 yellow-green demonstrating the formation of AgI within the zeolite itself. The amount of iodide taken up was not confirmed, but theoretically the materials possess 220 mg of Ag/gram in the zeolite pellets and 350 mg of Ag/gram in the zeolite spheres which could bind to an equivalent 10 amount of iodide in the formation of silver iodide.

Example 4

Precipitation of AgI in a natural carbon source

15 Agar or gelatin at an appropriate concentration is prepared with water and a silver salt (silver nitrate), filled in glass or fused silica tubes and allowed to become a solid at room temperature. The glass tubes are 20 cut to the desired length and soaked in a solution of sodium iodide to create silver iodide trapped in the agar or gelatin phase of the tubing.

Example 5

25 Precipitation of AgI on solidified carbonaceous materials and silica substrates

Natural carbonaceous sources such as wooden toothpicks and 30 rice grains, and glass tubing were first coated with a silver coating by adding the articles to solution A: a 7% solution of sodium carbonate, and mixed well for a few minutes. Then an equivalent amount of the following solution mixture was added and allowed to mix at room 35 temperature for five minutes: solution B: 0.72% silver nitrate, 0.72% ammonium nitrate, and 1.31% formaldehyde.

The articles were removed and air dried. The articles had a dull to shiny silver coating. After drying, the articles were immersed in a NaI solution with potassium ferricyanide and mixed well. After ten minutes, the 5 articles were removed. The silver coating now had a yellow-green colour denoting formation of silver iodide.

Example 6

10 Solution A is prepared as a 7% solution of sodium carbonate in water.
Solution B is prepared as 0.72% silver nitrate, 0.72% ammonium nitrate, and 1.31% formaldehyde in water.
Solution C is prepared as 1.0% NaI solution and 2.0% 15 potassium ferricyanide solution in water and contains 600 mCi of ^{125}I .

A 5 mm piece of carbon yarn 0.076 mm diameter obtained from Alpha Aesar in 5 metre lengths is placed in an 20 aliquot of solution A. To this is added an aliquot of solution B at room temperature. After about 5 minutes, the silver-coated carbon yarn is isolated by filtration, air-dried, and immersed in an aliquot of solution C for not less than 30 minutes. The excess solution is removed 25 by aspiration, and the now-radioiodine-containing yarn is dried in a stream of nitrogen.

Example 7

30 The method of Example 1 is repeated using $^{125}\text{I}^-$.

Example 8

The method of Example 2 is repeated using $^{125}\text{I}^-$.

Example 9

The method of Example 3 is repeated using $^{125}\text{I}^-$.

5 Example 10

The method of Example 4 is repeated using $^{125}\text{I}^-$.

Example 11

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The method of Example 5 is repeated using $^{125}\text{I}^-$.

Example 12

15 7-Iodo-8-quinolinol is prepared from 5-amino-8-quinolinol via a Gattermann reaction according to the method of Gershon et al (J. Heterocycl. Chem., 1971, 8(1), 129-131) by treatment of the amine with sodium nitrite to permit covalent attachment of ^{125}I in the presence of copper and 20 H^{125}I which is formed from Na^{125}I at the pH of the reaction. The reaction product is extracted into a small volume of methylene chloride. A piece of carbon yarn 0.076 mm in diameter and 5 mm long (from Alpha Aesar) is heated in a tube furnace above 400 °C in an argon flow, cooled in the 25 absence of moisture and added to the methylene chloride solution. The solvent is allowed to evaporate to leave the reaction product adsorbed on the carbon yarn. The yarn is placed in a titanium can and the can is sealed to form a seed suitable for use in brachytherapy.

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Example 13

35 Anthranilic acid is diazotized and treated with K^{125}I according to the method of Friedman L. and Logullo F.M. (Angew. Chem., 1965, 77, 217) to provide a mixture of products comprising radioactive iodinated aromatic organic

compounds. This mixture is adsorbed onto carbon yarn according to the method of Example 12.

Example 14

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Absorbance of Iodine-125 onto Naturally Occurring Material

A naturally occurring carbonaceous substance, rice grains, was subjected to a silver plating process followed by 10 reaction with a solution of sodium iodide containing iodine-125. The grains were shown to absorb the radioactivity.

Experimental.

15 1. Material Selection. Four rice samples were obtained, (these are detailed in Table 1 below) and a sample of each was weighed out and put into separate beakers. 10 mls of Sodium Carbonate solution (Solution 1, Table 2) were added to each beaker. The samples were 20 mixed using a magnetic stirrer and flea for 1 minute. The samples were dried and weighed. The results are reported in Table 3. The stirring was repeated using the same samples and fresh solution for a further 2 minutes; it was observed that all samples showed 25 signs of deterioration, and that these were most marked in samples 1 and 4.

The experiment was repeated with fresh rice grains and solution and stirring was continued for 5 minutes 30 by hand using a plastic stirrer rod to minimise damage. The samples were dried and weighed, and the results are shown in Table 4. Rice samples 1 and 4 still showed signs of damage.

35 2. Non-Radioactive Procedure. Rice samples 2 and 3 were selected for this section of the experiment based on

results from section 1. Aliquots of each of the rice samples were weighed out and put into 25 ml beakers; 10 mls of solution 1 was added and they were stirred for 5 minutes by hand. 10 mls of a silver nitrate, 5 ammonium nitrate, formaldehyde solution (solution 2) were added to each beaker and the mixture stirred for a further 5 minutes. The samples were observed to turn black, the samples were dried and weighed, and the results are reported in Table 5. The samples 10 were returned to clean 25 ml beakers and 10 mls of solution 3 were added and the mixture stirred for 5 minutes. The samples were dried and weighed, and the results are reported in Table 5.

15 On the basis of this experiment rice sample 3 was selected for further testing. It gave the highest absorbance of chemicals whilst retaining the greatest physical integrity.

20 3. Radioactive Procedure. An aliquot of rice sample 3 was weighed out and put into a glass vial. 10 mls of solution 1 was added and the container rotated on a vial rotator for 5 minutes. 10 mls of solution 2 were added and mixing continued for a further 5 minutes. The supernatant was removed and retained. 25 The sample was allowed to dry and then it was weighed; the results are recorded in Table 6. The sample was replaced in the vial, 10 mls of solution 3 containing 10 μ l of an iodine-125 solution containing 10 μ Ci per ml were added and the mixture rotated for 10 minutes. The supernatant was removed and retained. The samples were dried. 20 separate grains were selected, the radioactive content was determined on a gamma counter. The grains were 30 individually weighed. The results are given in Table 35 2.

4. Repeats.

5 4.1 The above experiment was repeated but with the radioactive content of solution 3 increased tenfold. The results are recorded in Table 8.

4.2 The experiment in 3 was repeated with a smaller sample of rice, reduced volume of solution 3 and the same radioactive content as in 4.1. The results are recorded in Table 9.

10

The initial tests were designed to identify the most favourable support for the experiments. Brown rice was indicated as the most robust whilst absorbing the greatest amount of iodide. The radioactive tests 15 were intended to investigate the potential for iodine-125 absorption.

Test 1. Nominal radioactive concentration. 0.1 μ Ci per 10 mls of Iodide Solution.

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Total Activity of Grains	14079.9 CPM (counts per minute)
Weight of Grains	0.4238 g
Absorption of iodine-125	34922 CPM/g

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Test 2. Nominal radioactive concentration. 1.0 μ Ci per 10 mls of Iodide Solution.

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Total Activity of Grains	181574.4 CPM
Weight of Grains	0.4731 g
Absorption of iodine-125	383797 CPM/g

Test 3. Nominal radioactive concentration. 1.0 μ Ci per 5 mls of Iodide Solution.

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Total Activity of Grains	760616.2 CPM
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Weight of Grains	0.5189 g
Absorption of iodine-125	1465824 CPM/g

5 The absorbance of iodine-125 shows an increase over the three experiments. The specific activity of the Iodide solutions is in the ratio 1:10:20.

10 The study indicates that the material absorbs iodine-125 in an apparent correlation to the specific activity of the iodide solution used for the process.

Table 1. Rice Samples

15 1. White Basmati.
2. Yellow Basmati.
3. Brown.
4. Arborio.

20 Table 2. Reagent Solutions

1. 7% Sodium Carbonate in aqueous.
2. 0.72% Silver Nitrate, 0.72% Ammonium Nitrate, 1.31% Formaldehyde in aqueous.
25 3. 1.0% Sodium Iodide, 2.0% Potassium Ferricyanide in aqueous.

Table 3. Absorbance of Sodium Carbonate solution One Min stirring

Rice Type No.	Initial Weight	After Soln. 1 Min	Increase
1	1.0050	1.0321	0.0271
2	1.0135	1.0743	0.0608
3	1.0099	1.0745	0.0646
4	1.0178	1.0928	0.0750

Table 4. Absorbance of Sodium Carbonate solution 5 Min stirring

Rice Type	Initial Weight	Weight after stirring	Increase
1	1.7358	1.7942	0.0584
2	1.8321	1.9682	0.1361
3	1.8010	1.9180	0.1170
4	1.8919	2.1339	0.2420

5

Table 5. Absorption of Silver and Iodide

Rice Type	Initial Weight	After Silver	After Iodide
2	1.6969	1.8403	1.9918
3	1.3952	1.5274	2.1464

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Table 6. Absorption of Silver prior to Radioactive test

Rice Type	Initial Weight	Weight after Silver Absorption
Brown	1.6372 g	1.7845 g

Table 7. Results from First Radioactive test

Grain Identity	Weight	CPM
1	0.0202	594.1
2	0.0285	758.1
3	0.0185	626.1
4	0.0258	808.2
5	0.0204	848.6
6	0.0201	564.1
7	0.0236	936.2
8	0.0166	486.1
9	0.0231	828.2
10	0.0225	656.2
11	0.0242	808.2
12	0.0211	714.2
13	0.0202	576.2
14	0.0212	814.2
15	0.0251	946.3
16	0.0115	498.1
17	0.0207	686.2
18	0.0221	692.2
19	0.0196	662.2
20	0.0188	576.2

Table 8. Results from Second Radioactive test

Grain Identity	Weight	CPM
1	0.0216	8257.7
2	0.0208	8821.8
3	0.0221	9151.9
4	0.0256	9141.6
5	0.0251	9186.9
6	0.0224	9267.9
7	0.0261	12606.1
8	0.0256	8781.1
9	0.0207	7105.4
10	0.0196	7865.4
11	0.0226	8272.2
12	0.0229	9474.7
13	0.0303	11221.8
14	0.0241	8625.1
15	0.0217	7212.5
16	0.0265	10096.3
17	0.0204	9840.7
18	0.0261	9591.3
19	0.0208	7733.2
20	0.0281	9320.8

Table 9. Results from Third Radioactive test

Grain Identity	Weight	CPM
1	0.0016	20684.8
2	0.0208	33899.1
3	0.0169	29333.9
4	0.0226	31055.3
5	0.0135	16084.8
6	0.0180	27555.5
7	0.0220	28080.8
8	0.0200	20936.9
9	0.0247	42486.6
10	0.0193	21551.1
11	0.0224	21912.7
12	0.0207	24429.9
13	0.0185	31040.8
14	0.0180	24250.1
15	0.0151	27447.4
16	0.0153	27522.1
17	0.0241	39403.9
18	0.0212	23690.7
19	0.0171	21406.3
20	0.0231	35611.5
21	0.0167	28079.1
22	0.0222	